



Email

## International Tungsten Industry Association

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Dr Ruth Lunn  
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Dear Dr Lunn,

**Re: Technical Comments on Draft Substance Profile for Cobalt-Tungsten, Carbide Powders and Hardmetals**

On April 22, 2010, the National Toxicology Program (NTP) published in the Federal Register (Volume 75, Number 77) the availability of, and request for comment on, the Draft Substance Profile for the *12th Report on Carcinogens (RoC): Cobalt-tungsten carbide: powders and hard metals*. The Health, Safety & Environment Committee of the International Tungsten Industry Association (ITIA) has developed comments on the Substance Profile. The ITIA is registered under Belgian law as a not-for-profit association with scientific purposes in support of the tungsten industry. ITIA's members are based in 17 countries (including the US) and include mining companies, processors/consumers, trading companies and assayers, as well as the world's leading manufacturers, importers, and users of hardmetal.

This letter provides technical comments developed and submitted on behalf of the ITIA, and reiterates several comments we have previously submitted to the NTP on three separate occasions:

- 1) Notification of nomination of "Cobalt/Tungsten-Carbide Hard Metal Manufacturing" for listing in the Report on Carcinogens (2004);
- 2) *Draft Background Document for Cobalt-Tungsten Carbide: Powders and Hardmetals* (2008); and,
- 3) *Expert Panel Report and Listing Recommendation for Cobalt-Tungsten Carbide Powders and Hard Metals* (2009).

The primary concerns we have consistently expressed to the NTP with the listing of "cobalt-tungsten carbide powders and hard metals" in the 12<sup>th</sup> RoC are as follows:

- the epidemiological data used to support the listing are limited, weak and inconclusive;
- there are currently underway a number of significant, multimillion dollar studies that will provide new data that could substantially influence the scientific basis for listing cobalt-tungsten carbide powders as reasonably anticipated to be human carcinogens.

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Additionally, subsequent to our latest comments to the NTP, the ITIA was made aware of a comprehensive animal inhalation bioassay on cobalt, tungsten carbide (WC) and the mixture of the two conducted in both rats and mice. One of the studies' primary investigators, Dr. Raymond Kutzman, provided us with a copy of the report for our review. However, we do not believe that the NTP or any of its expert panels have included this study in their consideration of listing cobalt-tungsten carbide: powders and hardmetals.

These concerns are summarized in further detail below in connection with specific statements contained in Draft Substance Profile.

**1. As acknowledged in the Final Background Document (2009), and the Substance Profile (2010), the epidemiological evidence for the carcinogenicity of cobalt-tungsten carbide powders is limited, very weak, and cannot support, on its own, that this material is a human carcinogen.**

There are no cancer bioassays for tungsten, tungsten carbide, or cobalt-containing tungsten carbide powders in the published literature. As such, epidemiological studies take on additional importance as key evidence of the carcinogenicity of tungsten containing compounds in humans. However, as noted several times in the Draft and Final Background Document, and in the Substance Profile, the epidemiological data on cobalt-tungsten carbide powders is extremely limited. These studies included (1) a cohort study of Swedish workers at three hard-metals facilities (Hogstedt and Alexandersson, 1990), (2) a small cohort of French hard-metal manufacturing workers (Lasfargues *et al.*, 1994), (3) a multi-plant cohort study of workers at 10 hard-metal producing factories in France, which also included a nested case-control analysis (Moulin *et al.* 1998), and (4) a cohort study of the largest factory (a single facility) from the multi-plant French study (Wild *et al.* 2000).

Although the Draft Substance Profile highlighted the four cohort studies of cobalt-tungsten carbide hardmetal manufacturing workers, only 3 studies are of sufficient size to have the power to detect any significant excess in cancer mortality. Also, these four studies were not independent. As noted in the Final Background Document: "The populations in the three French studies overlapped to some extent, as the cohort followed by Moulin *et al.* from 1968 to 1991 included most of the populations followed by Lasfargues *et al.* from 1956 to 1989 and Wild *et al.* from 1968 to 1992."

This was more clearly explained in the original draft of the Background Document (2008):

*Thus, if we are looking for completely independent observations, one should either contemplate these two papers [ Lasfargues *et al.* and Wild *et al.* ] and dismiss the paper by Moulin *et al.* (1998) or, alternatively, dismiss them and consider only the paper by Moulin *et al.* (1998).*

The limitations of the epidemiological data are not as clearly described in the Substance Profile, and may lead the reader to the incorrect conclusion that there was a high degree of independence among the 3 studies, when in fact, to a larger degree, these studies were multiple analysis of many of the same workers. Also, the summary of these studies provided in the Substance Profile lacks the in depth analysis that would permit the reviewer from independently assessing the significance of the findings relative to exposure and lung cancer.

For example, the Substance Profile states that "Positive exposure-response relationships were observed for all four measures of exposure: duration ( $P_{trend} = 0.03$ ), unweighted cumulative dose ( $P_{trend} = 0.01$ ), frequency-weighted cumulative dose ( $P_{trend} = 0.08$ ), and exposure level ( $P_{trend} = 0.08$ )." However, this simplistic summary is misleading. While there was a positive trend identified for exposure level, only the lowest of the "levels" (2-3) exhibited a statistically significant elevated OR (3.37; 95%CI= 1.19-9.56). The two other higher level groups (4-5 and 6-9) were not

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significantly elevated. Additionally, the 4-5 group had the largest number of lung cancers (19 compared to 8 in the 2-3 and 8 in the 6-9 groups), and one would expect that if this effect was causal, this group would have been statistically significantly elevated. However, this group had the lowest OR (1.54; 95%CI= 0.76-3.12). As such, these data do not indicate a dose-response relationship, and call in to question the purported association between hardmetal exposure and lung cancer.

Other critical limitations of the hardmetal epidemiological data were previously detailed by the ITIA and submitted to the NTP during the nomination/public comment process.

**2. Currently there are three (3) significant, multimillion dollar studies underway that will provide new data that could substantively influence the scientific basis for listing cobalt-tungsten carbide powders as reasonably anticipated to be human carcinogens. Two of these studies are being conducted by the NTP (cobalt and tungsten) and a third is a publicly-funded international epidemiological investigation of hardmetal workers.**

As part of both written and oral comments on the Draft Background Document, the ITIA highlighted the fact that there are several important in-progress studies that will have a significant impact on the determinations of the human carcinogenicity of cobalt-tungsten carbide powders. All of these studies are funded by independent governmental organizations, and represent a substantial advancement in the understanding of the toxicity on human carcinogenicity of tungsten and tungsten containing compounds.

These multimillion dollar studies include:

- 1) **Cobalt (cobalt metal powder):** Long-term carcinogenicity, 2 year inhalation study in mice (B6C3F1) and rats (F344). Exposure portion has been completed, histopathology currently being evaluated. This study is being conducted by the NTP.
- 2) **Tungsten (sodium tungstate dihydrate):** Long-term carcinogenicity, 2 year drinking water exposure in mice (B6C3F1) and rats (Harlan Sprague-Dawley). "Short-term" toxicity studies (13 week exposures) have been completed. The results of the short-term studies will be used to refine the long-term (2 year) carcinogenicity study. Multiple "special studies" including ADME and immune-toxicology studies in female B6C3F1 mice exposed via drinking water, and a standard 90-day drinking water study in male and female B6C3F1 mice are underway. These studies are being conducted by the NTP.
- 3) **Tungsten carbide-cobalt powder:** An international epidemiological study of hardmetal workers is currently underway. This investigation is being conducted by scientists from the University of Pittsburgh and the University of Illinois at Chicago. The investigation, supported by governmental funds, is focused on assessing the effect of work place exposure to tungsten carbide-cobalt powder on cancer mortality, with a particular focus on lung cancer.

The epidemiological investigation involves over 25,000 workers at 18 facilities in 5 countries, including the United States, Austria, Germany, Sweden, and the United Kingdom. The study is expected to be completed in 2012. The study is now in Phase 3, with site visits, data collection and data processing ongoing for the US portion of the study. The US portion will take three years to complete. Funding is presently being provided by a Pennsylvania Department of Health grant through 2011 Q2. A request has been submitted for federal funding to provide support for the final stages of the project. Backup funding options are also being explored by participating industry representatives. In the EU, the Austrian portion of the study has recently received government funding and study planning will begin in June. It is expected that the Swedish portion will be funded via governmental grants, with work beginning in 2011.

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**3. A comprehensive animal inhalation bioassay on cobalt, tungsten carbide (WC) and the mixture of the two was conducted in both rats and mice under contract to the NTP (1986). The results of this study lead to the conclusion “that neither WC, Co or the combination of the two is markedly toxic” in either species.**

The Substance Profile states that “no studies in experimental animals were identified that evaluated the relationship between cancer and exposure specifically to cobalt-tungsten carbide powders or hardmetals.” While this is true in terms of a specific cancer bioassay, in 1986, a study was conducted by Brookhaven National Laboratory on behalf of the National Toxicology Program (NTP), which evaluated inhalation exposure to a cobalt-tungsten carbide mixture. The results of this study are contained in the report entitled *A Study of Fischer-344 Rats and B6C3F1 Mice Exposed to Cobalt and/or Tungsten Carbide Dusts for Three Months* dated February 1986.

Rats or mice were exposed whole body to either filtered air, 1.0 mg cobalt/m<sup>3</sup>, 15 mg tungsten carbide/m<sup>3</sup>, or a combination of 1.0 mg Co plus 15 mg WC/m<sup>3</sup> for 6 hours/day, 5 days/week, for 62 days. Some of the endpoints evaluated in this extensive study include: “General Toxicological Endpoints” (body weight, organ weight, organ-to-body weight ratios); pathology examination (along with lung, all significant organs were taken and evaluated for evidence of exposure-induced pathology); hematology (hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin). In terms of gross pathology, there were no apparent changes in the lungs of male or female mice, and no evidence of pre-neoplasia, although low incidences of some pathology (e.g., focal hemorrhage, lymphoid proliferation) were observed.

The investigators concluded:

*Exposure to Co and WC and the mixture of the two chemicals at the concentrations tested did not produce a marked toxic response. No hematological values in either species were altered. Nor, for the most part, were significant changes in functional variables noted.*

However, the authors did caution there were observed compositional and histological changes and there was clearly a mild incipient or ongoing disease process in these lungs when the exposure was terminated. The significant pathology scores were observed only in the groups exposed to high dust levels (15 mg/m<sup>3</sup>) and may be related to the overall dust burden and not to the specific chemical. They hypothesized that with continued exposure these could progress to include functional impairment (Drew and Kutzman, 1986).

This study certainly provides valuable information with regard to the toxicity and carcinogenic potential of cobalt-tungsten carbide powders, but was not included in the Background Document, the Expert Peer-Review Panel Report, or the Draft Substance Profile. While the study did not follow standard NTP protocols for evaluating carcinogenicity via the inhalation pathway, it does fill an important data gap and should be considered prior to listing cobalt-tungsten carbide powders in the Report on Carcinogens.

## **Closing**

In conclusion, the ITIA recommends that the Board of Scientific Counselors defer any decisions regarding the listing of “Cobalt-tungsten carbide: powders and hard metals” in the 12<sup>th</sup> Report on Carcinogens until the ongoing studies on cobalt metal powder, tungsten, and hardmetal are completed. Such delay is without significant risk to workers currently employed in the hardmetal industry, the only potentially exposed population, since occupational exposure controls and appropriate work place practices are well established.

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As continually noted in the various NTP documents, and previous comments from the ITIA, the data upon which a decision for listing is to be made is extremely limited. Several ongoing studies will provide a substantial amount of new, and we suspect, clarifying information to assist the BSC in their important deliberations. And finally, perhaps the only animal inhalation bioassay on cobalt, tungsten carbide (WC) and the mixture of the two has been ignored during the NTP deliberative process.

Since the NTP would be the first US health organization to classify the carcinogenic status of cobalt-tungsten carbide powders and hard metals, we recommend that the NTP wait until all of the soon-to-be available data can be considered.

Yours sincerely,  
[Redacted]

Michael Maby  
*Secretary-General*